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Transmucosal drug administration as an alternative route in palliative and end-of-life care during the COVID-19 pandemic

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ARTICLE INFO

Article history:

Received 23 September 2020

Received in revised form 25 October 2020

Accepted 27 October 2020

Available online 1 November 2020

Keywords:

Benzodiazepine
Buccal
End-of-life drug
Intranasal
Opioid
Rectal
Sublingual
Systemic delivery

ABSTRACT

The Coronavirus disease 2019 (COVID-19) pandemic has led to a surge in need for alternative routes of administration of drugs for end of life and palliative care, particularly in community settings. Transmucosal routes include intranasal, buccal, sublingual and rectal. They are non-invasive routes for systemic drug delivery with the possibility of self-administration, or administration by family caregivers. In addition, their ability to offer rapid onset of action with reduced first-pass metabolism make them suitable for use in palliative and end-of-life care to provide fast relief of symptoms. This is particularly important in COVID-19, as patients can deteriorate rapidly. Despite the advantages, these routes of administration face challenges including a relatively small surface area for effective drug absorption, small volume of fluid for drug dissolution and the presence of a mucus barrier, thereby limiting the number of drugs that are suitable to be delivered through the transmucosal route. In this review, the merits, challenges and limitations of each of these transmucosal routes are discussed. The goals are to provide insights into using transmucosal drug delivery to bring about the best possible symptom management for patients at the end of life, and to inspire scientists to develop new delivery systems to provide effective symptom management for this group of patients.

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1. Introduction

Patients receiving palliative care require medications to alleviate symptoms such as pain, breathlessness, nausea and vomiting, anxiety and terminal restlessness [1,2]. However, as patients start to lose the ability to swallow medication, the oral route of drug administration becomes problematic. Studies have demonstrated that the need for alternative routes of medication increases in patients near the end of life, up to 70% of patients requiring a non-oral route of opioid administration [3–5]. Parenteral routes, including both intravenous and subcutaneous injection, provide rapid and effective drug delivery for symptom management. However, during the COVID-19 pandemic, the parenteral route has also become problematic due to the need for social distancing, and the potential limited availability of healthcare professionals to visit patients promptly to administer medications for distressing symptoms that may arise as death approaches. This is particularly difficult in community settings where patients are more dependent on drug administration by doctors or nurses visiting at home.

Transdermal and transmucosal routes are important alternative routes of administration in palliative care. Transdermal route involves the permeation of drug across the skin layers into the systemic circulation. It is frequently used in pain management in home palliative care due to the ease of application, especially when patients are no longer able to swallow [6]. However, the slow absorption rate has limited its indication to chronic/background pain only and renders it unsuitable for breakthrough pain which requires rapid onset of action [7,8]. On the other hand, transmucosal drug administration, which refers to the absorption of drug through the mucosal epithelium into the systemic circulation, offers more diverse pharmacokinetic profiles. Intranasal, oral transmucosal and rectal routes are the major transmucosal routes that are already used in palliative care as alternatives to oral and parenteral drug administration for some drugs [4]. However, the transmucosal routes of administration are generally underappreciated, and they are not commonly used in adult practice. There are insufficient studies to reveal the usage of transmucosal formulations in palliative care. Some doctors, nurses and caregivers are not familiar with the principles of these delivery routes and are therefore uncertain about their efficacy [9]. Lack of clear guidance and local availability within hospital formularies are identified as barriers to their wider use [10,11]. Nevertheless, there is growing experience in paediatric palliative care practice, allowing the benefits of needle-free drug administration by family caregivers at home.

This review presents an overview of the transmucosal routes of drug administration, their merits, challenges and limitations. It is our goal to provide insights into palliative care symptom management using

transmucosal drug delivery so that the best possible care to patients at the end of life can be given especially during the COVID-19 pandemic. We also aim to inspire formulation scientists to develop new delivery systems that can ease the symptoms of this group of patients safely, rapidly, effectively and comfortably, thereby optimising their quality of life at the end of their lives.

2. Transmucosal drug delivery

Transmucosal drug administration is an attractive alternative to oral and parenteral routes of administration, due to its non-invasive nature, and offering the possibility of self-administration, or administration by lay caregivers. It can reduce or completely bypass first-pass metabolism, avoid gastrointestinal degradation and provide rapid onset of action [12–14]. However, not all the drugs can cross the mucosal epithelium effectively. To identify drugs that are suitable for transmucosal delivery, it is essential to first understand the mechanism of mucosal drug absorption. While the intranasal, oral and rectal mucosa have their own unique anatomical and physiological characteristics, they share some common properties. For instance, mucus is a universal delivery barrier at the mucosal surface, and drugs are usually absorbed through the mucosa into the systemic circulation through either the transcellular or paracellular route. The characteristics of different mucosal epithelium are summarised in Table 1.

2.1. Mucus

The presence of a mucus layer lining on the mucosal epithelium presents a barrier to transmucosal drug delivery [15]. The major functions of mucus are to provide lubrication and protection to the

Table 1
Properties of different mucosal surfaces for transmucosal drug delivery.

Characteristics	Nasal	Oral		Rectal
		Buccal	Sublingual	
Surface area	130 cm ²	50 cm ²	25 cm ²	200–400 cm ²
Villa/microvilli	Present		Absent	Absent
Thickness of mucosa	700–1000 μm	500–800 μm	100–200 μm	~ 800 μm
Volume of fluid	~0.1 ml		~1 ml	1–3 ml
pH of mucosal environment	5.0–7.8		5.5–7.0	7.0–8.0
Mucus thickness	10–15 μm		70–100 μm	~ 150 μm
First pass metabolism	No		No	~50% bypass

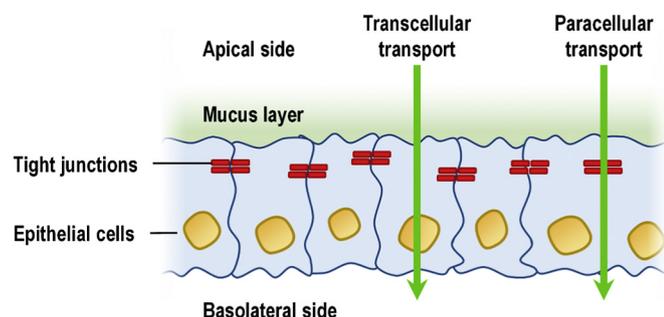


Fig. 1. Schematic diagram of the routes of drug transportation across the epithelium.

underlying epithelium. Mucus is mainly composed of water (~95%) and mucin (~ 2 to 5%), with a small amount of globular proteins, lipids, DNA and cell debris [16]. Mucin is a high molecular weight (10–40 kDa) glycoprotein which gives rise to the viscoelastic property of mucus. The mucin fibres form an entangled network which acts as a physical barrier to drug penetration. Due to the hydrophobic domains and the negatively charged sialic acid and sulphate groups in the mucin glycoprotein, the mucus also creates an interactive barrier that limits drug diffusion. Moreover, since mucus is continuously produced, secreted, shed, and discarded [17], molecules that fail to penetrate the mucus layer are eventually removed by mucus clearance before they can reach the epithelial cells [18]. The pore size between the mucus mesh network is around 20 to 1800 nm, varying greatly between different sites and disease states [15]. In general, small molecules that have minimal interaction with the mucus networks (i.e. molecules with a hydrophilic surface and electrically neutral) are more likely to diffuse across the mucus barrier successfully [18].

2.2. Transcellular and paracellular routes

After a drug is deposited on the mucosal surface, it may cross the epithelium via the transcellular or paracellular route (Fig. 1). The former refers to drug permeation *through* the cells while the latter refers to drug permeation *between* adjacent cells [19]. Both routes belong to a passive transport process driven by a local concentration gradient. Whether a drug molecule can cross the epithelium and which route it takes are dependent on its intrinsic physicochemical properties [20]. Hydrophilicity/lipophilicity, molecular weight and degree of ionisation are the three major determinants. Lipophilic molecules can diffuse freely through the phospholipid bilayers of the cell membrane and therefore prefer the transcellular route. On the other hand, hydrophilic molecules cannot diffuse across the cell membrane, hence the paracellular route

becomes significant to these molecules. However, the tight junction between adjacent cells limits the efficacy of this route of transportation [21]. The smaller the molecules, the more effectively they can permeate through the tight junction. The degree of ionisation is dependent on the pKa of the drug and the pH of the environment. Only the non-ionised species of a drug can permeate (by drug partitioning) through the cell membrane effectively, and this affects mainly the transcellular route. In general, small lipophilic molecules that are non-ionised at their surrounding pH are favourable for transmucosal absorption. Apart from the three aforementioned properties, aqueous solubility and dose of drug can also influence its absorption. However, absorption also relies on the volume of fluid available at the site of administration for drug dissolution to take place, hence the exact properties of a drug required in order to achieve effective transmucosal delivery is specific to each route of administration. The physicochemical properties of drugs used in transmucosal delivery are summarised in Table 2 to illustrate the desirable properties. They typically have small molecular weight (<500 Da) with a high log *P* value (>2.0).

2.3. Penetration enhancers

Only a small number of drugs exhibit the desirable physicochemical properties to cross the mucosal epithelium effectively. In order to enhance drug absorption, penetration enhancers (or permeation enhancers) are commonly investigated in the development of transmucosal formulations to overcome the epithelial barrier, especially in intranasal, buccal, and to a lesser extent, rectal formulations [46]. Penetration enhancers promote drug absorption by increasing the permeability of epithelium. They are particularly useful in the delivery of large molecules such as proteins and peptides but can also improve the delivery of hydrophilic and/or ionised small drug molecules [19,47–49]. The most important class of penetration enhancers is surfactant such as bile salts (e.g. sodium deoxycholate), fatty acids (e.g. oleic acid) and phospholipids. Their mechanisms of action include extraction of membrane proteins and lipids, perturbing the lipid packing in epithelial cell bilayer and modulation of tight junctions [47,50]. Other penetration enhancers such as cationic polymers (e.g. chitosan), chelators (e.g. ethylenediaminetetraacetic acid) and tight junction modulators (e.g. occludin) are also being studied [21,51]. The major concern with the use of penetration enhancers is toxicity which may damage the structural integrity of the epithelium irreversibly, leading to enhanced permeation to harmful chemicals and microorganisms. In fact, most of the penetration enhancers are still under investigation. To allow more drug candidates to be successfully delivered through the transmucosal route, it is important to identify suitable enhancer that exhibits transient permeation effect for the drug concerned with minimal local irritation and toxicity.

Table 2

The summary of the physicochemical properties of selected drugs that are reported in the literature to be delivered by transmucosal route in the clinic.

Drug	Log <i>P</i>	Molecular Weight (Da)	Transmucosal route
Butorphanol (Tartrate)	3.7	477.6	Intranasal [22,23]
Buprenorphine (Hydrochloride)	5.0	504.1	Buccal, Sublingual [24,25]
Diamorphine (Hydrochloride)	1.6	423.9	Intranasal [26,27]
Diazepam	2.8	284.8	Buccal, Rectal [28–31]
Fentanyl (Citrate)	2.3	528.6	Intranasal, Buccal, Sublingual [12,22,32]
Hydromorphone (Hydrochloride)	1.2	321.8	Intranasal [22,33]
Lorazepam	2.4	321.2	Intranasal, Sublingual [22,34,35]
Methadone (Hydrochloride)	3.9	345.9	Rectal [36]
Midazolam	4.3	362.2	Intranasal, Buccal, Sublingual, Rectal [37–39]
Morphine (Sulphate)	0.9	758.8	Rectal [40,41]
Oxycodone (Hydrochloride)	0.7	351.8	Rectal [42]
Sufentanil (Citrate)	4.0	578.7	Sublingual [43,44]
Tramadol (Hydrochloride)	3.0	299.8	Rectal [45]

Note: *P* is the octanol-water partition coefficient. The higher the log *P*, the more lipophilic it is. The values are obtained from Clark's Analysis of Drugs and Poisons and AHFS Drug Information.

3. Intranasal delivery

The intranasal route of administration has been widely used for the management of local symptoms such as nasal congestion and allergic rhinitis. Because of the relatively large surface area of the nasal cavity and the extensive vascularisation of the nasal mucosa, this route of administration has received increasing attention for systemic drug delivery. The fast onset of action and non-invasive administration also make the intranasal route particularly attractive for the management of acute pain and breakthrough pain in cancer patients [52–55]. It has great potential to be used as an alternative route of drug administration in palliative care.

3.1. Structural and physiological characteristics of nasal mucosa

The nasal cavity can be divided into three regions, namely vestibular, olfactory and respiratory regions (Fig. 2). The vestibular region is the anterior section of the nasal cavity, but since this region has limited vascularisation and small surface area (~0.6 cm²), its role in drug absorption is insignificant [56]. The olfactory region is located on the roof of the nasal cavity. The olfactory epithelium consists of three major cell types: basal cells that can differentiate into the required cell types to maintain the intactness of the epithelium; microvilli-bearing sustentacular cells that protect and support the olfactory cells; and ciliated olfactory cells that are responsible for the sense of smell and have direct access to the central nervous system (CNS), offering a possible route for nose-to-brain drug delivery [57]. This region is moderately vascularised, enabling it to contribute to systemic absorption, albeit a limited role due to a small surface area (~10 cm²). The respiratory region comprises the majority of the nasal cavity. It is responsible for filtering, warming and humidifying inhaled air. This region is mainly composed of columnar cells with microvilli and mucus-secreting goblet cells [58]. The nasal cavity is extended by the three folds of turbinate bones, also known as the conchae (superior, middle and inferior concha), which contribute to a large surface area of 130 cm² (excluding microvilli). The relatively large surface area and the highly vascularisation of nasal mucosa make it an attractive site for systemic drug delivery [20].

The cilia in the nasal cavity are covered in a mucus blanket of 5–15 μm thick [15,59]; they have a key role in airway defense by protecting the nasal epithelium against potentially harmful substances. The pH of nasal mucus could range from 5.0 to 7.8 [15] which may result in inconsistent drug ionisation, leading to variation in drug absorption. Since mucus usually contains a high content of water, it creates an effective barrier to lipophilic drugs which have limited diffusion across the mucus layer. Furthermore, the airflow of the nasal cavity is constantly

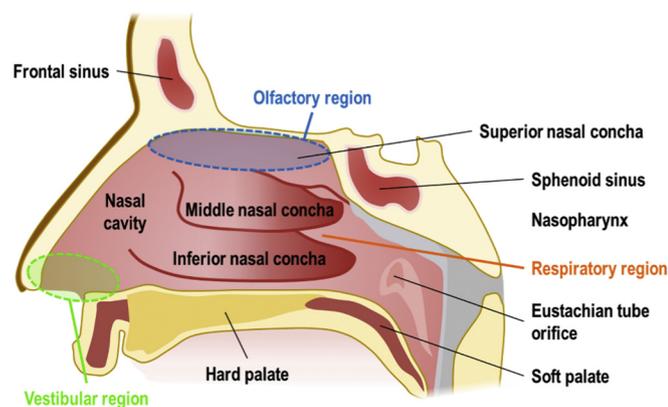


Fig. 2. Schematic diagram of the nasal cavity, depicting the vestibular, olfactory, and respiratory regions.

varying, suggesting that a mucoadhesive property of nasal formulation of drugs is desirable, to avoid incomplete dosage delivery.

Mucociliary clearance is another barrier to nasal drug absorption. It is a cleansing mechanism that protects the nasal mucosa by removing foreign substances that are trapped by the mucus lining. The beating cilia propel the mucus towards the nasopharynx and eventually oropharyngeal junction where it is swallowed [60]. Because of the rapid clearance rate (12 to 15 min), drugs deposited in the nasal cavity could be easily removed by mucociliary clearance. With the use of mucoadhesive excipients, nasal retention time and drug absorption could be improved [61]. One of the unique features of intranasal delivery compared to other transmucosal routes is its capability to deliver drug molecules directly into the CNS. This topic has been extensively reviewed elsewhere and is not discussed further here [56,57,62].

3.2. Drug absorption across nasal mucosa

Drug absorption across nasal mucosa involves both paracellular and transcellular transport. Once across the nasal mucosa, drug molecules directly reach the circulation, completely bypassing first-pass metabolism. However, local enzyme activity in the nasal cavity may reduce the bioavailability of the administered drug [20]. A number of enzymes have been identified in the intranasal lumen and epithelium, such as cytochrome P450, epoxide hydroxylase, protease and peptidase. In general, drug degradation in the nasal cavity is less significant than in the gastrointestinal tract, but the extent of degradation could be substantial for peptide and protein drugs [63].

3.3. Limitations of the intranasal route

The limited volume of fluid inside the nasal cavity, typically around 75 to 135 μl [64], renders drug dissolution very challenging. Moreover, nasal drug absorption can be easily affected by some minor ailments and disease conditions which alter the nasal environment. For example, rhinitis and local infection may lead to inflammation of the mucosa, resulting in hypersecretion that dilutes the drug concentration, influencing rate of drug absorption and the time for onset of action [65]. Treatment of rhinitis with a local vasoconstrictor was also reported to reduce drug absorption by restricting blood flow to the site of absorption [20]. Furthermore, it was observed that mucociliary clearance was disturbed in smokers and in patients with laryngectomy or diabetes mellitus [20,66], thereby changing the exposure of intranasally administered drugs, but the effect on drug absorption is unclear. While intranasal administration is usually well-tolerated, common side effects include nasal discomfort, congestion and local irritation. Table 3 summarises the advantages and disadvantages of intranasal drug delivery.

3.4. Intranasal formulations and dosage forms

3.4.1. Nasal spray

Nasal spray is the most common dosage form for intranasal drug delivery due to the ease of administration and efficient nasal deposition compared to drop instillation. With the nozzle of a spray bottle inserted into the nostril, liquid dosage forms (including solutions, suspensions and emulsions) are atomised into fine droplets for nasal deposition.

Table 3
Advantages and disadvantages of intranasal drug delivery.

Advantages	Disadvantages
<ul style="list-style-type: none"> • High vascularization • Rapid onset of action • Bypass first pass metabolism • Easy and self-administration 	<ul style="list-style-type: none"> • Mucociliary action • Enzymatic activity in nasal mucosa • Local irritation • Only small volume of dose can be administered • Variation in absorption (in mucosa alteration or administration of vasoconstrictive drug)

Particle size of $>10\ \mu\text{m}$ in aerodynamic diameter is required for particles to be retained in the nasal passageways, as smaller particles tend to deposit further down in the respiratory tract [67]. Isotonic (or slightly hypertonic) aqueous-based formulations at physiological pH (slightly acidic) are preferred, to avoid interference with the cleansing action of cilia and minimise local irritation. There is also a limitation of the volume of liquid that can be administered, typically up to $150\ \mu\text{l}$ per nostril. Viscosity modifying agents (e.g. methylcellulose) and mucoadhesive polymers (e.g. polyacrylic acid and thiomers) are sometimes added in the formulation to reduce nasal drip and runoff [61]. However, the formulation should not be too viscous, otherwise it may hinder the atomisation process. Penetration enhancers may also be included in the nasal formulation to improve drug absorption, but their association with cell toxicity have limited their use in the delivery of large molecules [68].

In order to increase the nasal residence time, some gel-based nasal spray formulations were developed to prolong the contact time with the nasal mucosa. One example is the fentanyl pectin nasal spray (FPNS) which was approved for breakthrough pain in adult patients with cancer [69]. Pectin, which is a plant-based polysaccharide, undergoes gelation in situ when in contact with calcium cations on the nasal mucosal surface [70]. The pectin nasal spray was found to demonstrate a lower decline in plasma drug level compared with other non-gelling nasal spray, suggesting that it can provide an extended analgesia effect [71].

Intranasal administration of parenteral formulations is sometimes practised in the clinic, especially during emergency situations, for patients who require rapid pain relief, sedation or treatment of seizures [72,73]. This approach is common in paediatric practice [27,74]. Drugs are administered intranasally through an atomisation device. For example, a mucosal atomization device (MAD) consists of a soft conical plug that forms a seal with the nostril to minimise liquid lost and a nozzle that generates a fine mist of particles with size suitable for nasal deposition [72]. However, not all parenteral formulations exhibit suitable properties (in terms of pH, tonicity and concentration) for nasal delivery, affecting toleration and drug absorption.

3.4.2. Powders

Powder dosage form has the advantage of better stability which is particularly attractive for peptides and proteins as cold-chain storage could be avoided. It also allows prolonged mucosal contact time which enhances drug absorption [75]. There are a few intranasal powder formulations available in the market, including sumatriptan for the treatment of migraine [76,77] and glucagon for use in hypoglycemic emergency [78]. Both these demonstrate good safety profile, fast absorption and rapid onset of action. Intranasal powder formulations of different drugs such as oxytocin and dihydroergotamine are also under development [79,80]. It has been suggested that powder formulation is more likely to trigger local irritation than its equivalent liquid formulation, a particular consideration in chronic use.

4. Oral transmucosal delivery

Oral transmucosal delivery refers to the systemic delivery of drug through the mucous membrane of the oral cavity. It is a popular route of drug administration used in palliative care compared to other transmucosal routes, due to its convenience and ease of administration [4]. It is further divided into the buccal route (in which the drug is absorbed via the buccal mucosa on the lining of the cheek and gum), and the sublingual route (in which the drug is absorbed via the mucosa of the ventral surface of the tongue and the floor of the mouth under the tongue). Different oral transmucosal dosage forms are available for the management of breakthrough pain, such as tablet, lozenge and oral film. However, patients in palliative care may also suffer from oral mucositis and xerostomia, which render the oral transmucosal route less effective [81]. It is also less desirable for patients who experience nausea

and vomiting. Nonetheless it is an important route of administration to provide rapid onset of action for palliative care populations.

4.1. Structural and physiological characteristics of oral mucosa

The composition and thickness of the oral epithelium depends on the site in the oral cavity. The buccal region refers to the lining of the cheek and has a surface area of $\sim 50\ \text{cm}^2$ [82]. The buccal epithelium is composed of non-keratinised stratified squamous epithelial cells of around 40–50 cells thick ($500\text{--}800\ \mu\text{m}$). The cells in the lower layers are constantly undergoing differentiation into larger and flatter cells as they approach the outer surface [83] (Fig. 3). The sublingual region refers to the floor of the mouth. Similar to the buccal epithelium, the sublingual epithelium is also composed of non-keratinised stratified squamous epithelial cells but with a thinner cell layer of 8–12 cells thick ($100\text{--}200\ \mu\text{m}$). Hence the sublingual mucosa has a higher permeability [84]. Other regions in the oral cavity such as the gingival and palatal epithelia are composed of keratinised cells with poor drug permeability, making them less suitable for drug delivery.

Saliva is produced by the parotid, mandibular and sublingual glands, as well as some minor salivary glands. It functions as a lubricant, protects the oral tissues from abrasion, assists the masticatory process, facilitates articulation of speech, and contributes to the mineralisation of the tooth enamel [85]. It is also involved in food digestion, containing digestive enzymes such as amylase and lipase which are responsible for the breakdown of starch and fat, respectively. The pH of the saliva plays an important role in keeping a balanced microbiota, and is maintained at around 5.5–7 [83]. Like other mucosal surfaces, the oral mucosa is coated with a thin layer of mucus which is part of the saliva. The mucus layer, which is $70\text{--}100\ \mu\text{m}$ thick, presents a barrier to drug absorption by impeding drug penetration [82].

4.2. Drug absorption across oral mucosa

For both buccal and sublingual routes, once the drug has overcome the mucus and epithelium barrier through either paracellular or transcellular diffusion, it can be absorbed via the venous drainage to the internal jugular vein and enter the systemic circulation directly, bypassing first-pass metabolism and gastrointestinal drug degradation [86]. Due to the relative thickness of the epithelium and the extent of vascularisation, the sublingual mucosa has a higher drug permeability and offers a faster onset of action than the buccal mucosa. On the

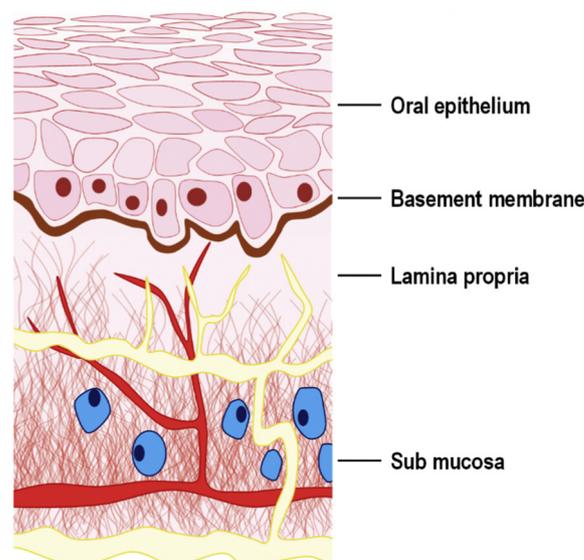


Fig. 3. Schematic diagram of the structure of oral mucosa.

other hand, the buccal route can be useful for extended drug release by increasing the mucosal adhesion time while it can still achieve a relatively rapid onset of action. The presence of saliva is crucial for drug absorption as it provides a medium for a drug to be released from the dosage form and dissolve. In general, the volume of saliva in the oral cavity is around 1 ml [87]. However, cancer patients often experience xerostomia (dry mouth) which impacts on drug absorption through the oral mucosa. On the other hand, excessive saliva, which is less common but happens to patients with Parkinson's disease and other neurologic disorders [85], could lead to a wash-out effect which also reduces drug absorption. Drug absorption is also largely dependent on the contact time with the mucosal surface. Since the oral cavity has a small surface area for drug absorption, this also limits the dose volumes that can be administered without being swallowed or aspirated.

4.3. Limitations of oral transmucosal route

While the administration of a drug via the oral mucosa is generally easy and convenient, it suffers several disadvantages, and is sometimes considered to be ineffective or not feasible in patients towards the end of their lives [88,89]. For example, terminal agitation is a common end-of-life symptom and agitated patients often cannot cooperate with taking orally administered medications including buccal and sublingual medications. This would cause additional distress to caregivers. The oral transmucosal route is also not as suitable for patients suffering from nausea and vomiting. As previously mentioned, drug dissolution and absorption could also be challenging in patients with a dry mouth condition. Formulations that are unpalatable or cause local irritation may lead to voluntary expulsion or swallowing. There is also a risk of choking and aspiration in young and elderly patients, and when patients are unconscious or uncooperative [82,90]. Table 4 summarises the advantages and disadvantages of oral transmucosal drug delivery.

4.4. Buccal and sublingual dosage forms

4.4.1. Buccal and sublingual tablet

Tablet is the commonest dosage form for oral transmucosal delivery, mainly because of its low cost of production and ease of administration. There are two major types of tablet formulations for oral transmucosal administration, namely orally disintegrating formulations and mucoadhesive formulations. Sublingual tablets usually belong to the former with properties such as short residence time, fast disintegration and dissolution in saliva without water consumption [91]. The goal of this type of formulation is to provide a rapid onset of action, usually within minutes. For example, buprenorphine and fentanyl are available as sublingual tablets for management of severe pain and breakthrough pain, respectively. For efficient transmucosal delivery and proper absorption via the oral mucosa, these types of tablets must not be swallowed but placed under the tongue or in the buccal cavity. To achieve rapid disintegration, super-disintegrants such as croscarmellose sodium and sodium starch glycolate are commonly included in the orally disintegrating tablet formulation. Effervescent tablets are also employed to provide rapid drug absorption through the oral cavity. One example is the fentanyl effervescent buccal tablet which contains

citric acid and sodium bicarbonate. Enhanced absorption of fentanyl is associated with the change of pH microenvironment in the buccal mucosa that leads to the formation of a non-ionised form of fentanyl, thereby facilitating drug absorption [92]. A mucoadhesive tablet is more commonly used for buccal administration, offering the possibility of extended release. For buccal administration, tablets are usually placed between the lip and gum or the mucosa of the cheek. The mucoadhesive property allows prolonged contact time with the oral mucosa and prevents the tablet from being dislodged from the site of application. Polymers such as polyacrylic acid (Carbomer), carboxymethylcellulose and sodium alginate are commonly used to achieve mucoadhesion [93,94]. Some early studies showed that a controlled release buccal tablet of morphine demonstrated a similar pharmacokinetics profile to the controlled release oral tablet [4,95,96].

4.4.2. Lozenge

Lozenges are usually placed between the cheeks and gums where drugs are absorbed through the buccal mucosa. The sucking action by patients promotes the release of the drug from the dosage form. However, a coordinated sucking could be difficult for young patient or patient with neuro-disability. The most notable lozenge formulation in the use of palliative care is the fentanyl lozenge which is used in breakthrough pain management. The fentanyl lozenge formulation is attached to an applicator for ease of administration and allows switching of sides in the mouth. The formulation is sweetened in order to enhance the palatability of the medication, although dental problems could be an issue with repeated use [97]. Some patients are reported as concerned with the 'childish appearance' when using this medication which resembles a lollipop [98]. The drug is usually released and absorbed within 15 min to obtain rapid pain relief [97].

4.4.3. Oral film

Oral film has become a popular dosage form in oromucosal delivery system development. It is usually applied inside the cheek for a drug to be absorbed through the buccal mucosa, although sublingual film is also available. It is sometimes referred to mucoadhesive buccal film or orodispersible film. The former may dissolve or be removed after drug release, while the latter is intended to disperse rapidly within the oral cavity, usually within 15 min [99]. Oral films typically consist of a mucoadhesive layer where the drug is dissolved, and a drug-free backing layer which acts to shield the drug from the oral cavity so that unidirectional drug release to the oral mucosa is achieved, reducing drug loss due to swallowing [100]. Polymers such as carmellose sodium and hydroxypropyl cellulose are commonly used to prepare the drug-containing mucoadhesive layer. The backing layer is either soluble or insoluble, depending on whether removal is required after drug release. Penetration enhancers are sometimes added to improve drug absorption. The size of an oral film varies, depending on the dose of the drug. For example, the size of the 200 µg and 800 µg fentanyl oral films are 0.78 cm² and 3.1 cm², respectively [100]. Oral films are ultra-thin (typically between 0.2 and 1 mm) to minimise discomfort caused to the patients. However, they should not be cut for dose adjustment as this may affect drug release and absorption rate. A number of oral film products are marketed, including fentanyl buccal soluble film, buprenorphine buccal film and buprenorphine/naloxone sublingual film.

4.4.4. Liquid and spray

Liquid dosage forms, including aqueous solutions and suspensions, are also employed for oral transmucosal delivery due to simple formulation [86]. They are more often seen in paediatric formulations to minimise the risk of choking [90]. For example, buccal midazolam solutions are used for the treatment of acute seizures in children and infants above three months old. They are packaged in prefilled syringes to avoid the need for dose measurement in an emergency. The biggest challenge of buccal liquid dosage form is facilitating retention of medications in the oral cavity. The liquid may easily be swallowed prior to

Table 4
Advantages and disadvantages of oral transmucosal drug delivery.

Advantages	Disadvantages
<ul style="list-style-type: none"> • Easy and self-administration • Bypass first-pass metabolism • Several dosage-form options 	<ul style="list-style-type: none"> • Small surface area for absorption • Limited dose and volume • May not be suitable in nausea and vomiting
<ul style="list-style-type: none"> • Rapid onset of action with possibility of extended release (buccal route) 	<ul style="list-style-type: none"> • Dissolution problem in patients with dry mouth condition • Taste could be an issue

transmucosal absorption. As a result, the dose of drug cannot be accurately controlled. Moreover, buccal liquids may lead to extra production of secretions, thus affecting drug absorption and patient's comfort. Mucoadhesive agents are therefore required to prolong the residence time. More recently, iontophoretic techniques have been investigated to enhance delivery of drug liquid across the oral mucosa [101]. Alternatively, sprays can be used to enhance drug deposition on the mucosal surface [86] and they have been used in nicotine replacement therapy and the delivery of glyceryl trinitrate in angina.

5. Rectal delivery

The rectal route of drug delivery has been used mainly for the treatment of local conditions such as constipation, infection and inflammation. As the rectal mucosa is highly vascularised, this route of administration is useful for rapid systemic drug absorption, particularly in an emergency or when the oral route is unavailable. Rectal formulations have been used in pain management [102,103], sedation [104] and treatment of seizures [105]. Compared to other transmucosal routes of administration, one of the distinct advantages of rectal delivery is that it is not limited by vomiting which patients commonly experience as they approach the ends of their lives. The rectal route may be more acceptable in paediatric practice, but it remains unpopular in many countries due to privacy and culture issues, and it is seldom used in palliative care especially for adult patients. Training and education are required for the potential for this route of administration to be realised.

5.1. Structural and physiological characteristics of rectal mucosa

The rectum is the distal part of the large intestine. It acts primarily as a temporary storage for faeces with a minor role in water absorption. It is approximately 15–20 cm in length. With the lack of villi or microvilli on the luminal surface, it has a relatively small surface area (200–400 cm²) in contrast to the small intestine (~2,000,000 cm²) for drug absorption [106]. The wall of rectum consists of a single layer of columnar epithelial cells together with the goblet cells. Towards the anus, the columnar epithelium undergoes an abrupt transition to non-keratinised stratified squamous epithelium at the anorectal junction and eventually to keratinised stratified squamous epithelium at the external anal sphincter [107]. The goblet cells are responsible for mucus secretion. The rectal mucus is composed mainly of water and mucin (<5%). The rectal mucus layer is around 150 µm thick [108] and it acts to lubricate and protect the rectal epithelium (e.g. during defecation) but at the same time it also presents a barrier for drug absorption [106]. The rectal fluid has a neutral pH of 7–8, which favours the absorption of drugs that are predominantly in their non-ionised form at this pH range. Since rectal fluid has a weak buffering capacity, formulations that change rectal pH may affect drug absorption by altering drug ionisation and may cause irritation to rectal mucosa. The small volume of rectal fluid (around 1–3 ml) also poses difficulty for drug dissolution [109].

5.2. Drug absorption across rectal mucosa

Similar to other transmucosal routes of delivery, drugs are absorbed rectally either via the paracellular or transcellular route, depending on their physicochemical properties. Although the rectum has a relatively small surface area for drug absorption, the environment of an empty rectum is relatively stable to achieve reproducible absorption [30]. The rectum is drained by the superior, middle and inferior rectal veins (Fig. 4). The fate of the absorbed drug is dependent on the site where absorption occurs [106]. Drugs absorbed at the upper rectum enter the superior rectal vein which drains through the mesenteric and portal veins into the liver. In contrast, drugs absorbed at the lower rectum enter the middle and inferior rectal veins which drain through the inferior vena cava directly into the systemic venous circulation, thereby avoiding first-pass metabolism. It has been reported that approximately 50% of

the dose of a drug can bypass the liver [106]. Compared to other parts of the gastrointestinal tract, the rectum has a much lower enzymatic activity, hence rectal degradation of drug is also relatively low. It is noted that rectal microbiota produces hydrolytic and reductive enzymes, which may affect drug metabolism [107,110].

5.3. Limitations of rectal route

Despite the merits of using the rectal route for systemic drug delivery, this route of administration is often neglected or avoided, mainly due to the lack of acceptance by patients and clinicians, privacy concerns, cultural barriers and the practical limitations of access, particularly outside home or hospital. Some clinicians may also perceive the rectal route as 'nonaggressive symptom management' or concern with the lack of clinical evidence for its efficacy [89,111]. In palliative care, it requires caregivers to be able or willing to administer drugs rectally, which they may be reluctant to do. The rectal route is difficult with patients who use wheelchairs; it may not be suitable for patients with rectal tumours, rectal bleeding, or those who have recently undergone bowel surgery [89].

Rectal drug delivery is often challenged by erratic drug absorption due to potential expulsion of the dosage form or poor adhesion to the mucosal membrane. Bioavailability may vary according to the site of drug absorption within the rectal cavity. Drug dissolution in the rectum is another issue due to the small volume of rectal fluid, and this problem is even more prominent in palliative care patients who are often dehydrated due to reduced fluid intake and opioid or anticholinergic medications [112]. Delayed drug absorption could lead to drug degradation caused by microbiota metabolism in the rectum, further decreasing the drug bioavailability [113]. Presence of faeces in rectum can also affect drug absorption and defecation would lead to expulsion of the drug. Table 5 summarises the advantages and disadvantages of rectal drug delivery.

5.4. Rectal formulations and dosage forms

5.4.1. Suppository

A suppository is a single-dose preparation for rectal administration. It is the most common rectal dosage form for systemic absorption for a wide range of indications including pain, seizures, sedation, nausea and vomiting. Suppositories are inserted into the rectum past the muscular sphincter to avoid falling out. Drugs are either dispersed or dissolved in a suitable base. There are two types of suppository base – lipophilic

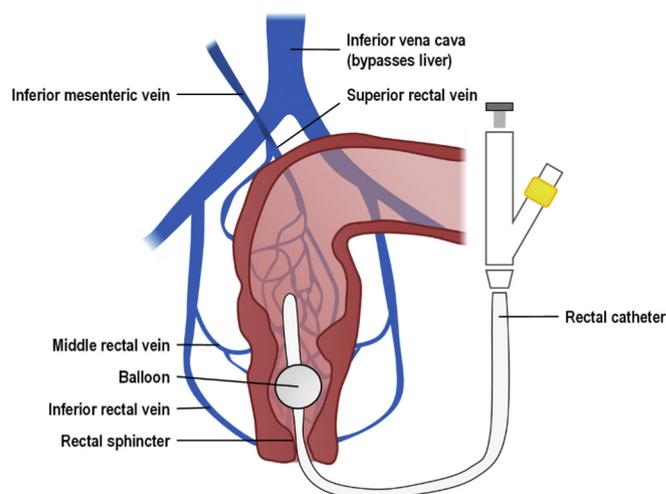


Fig. 4. Schematic diagram of the rectum with a rectal catheter inserted. The major veins of venous return are shown.

Table 5
Advantages and disadvantages of rectal drug delivery.

Advantages	Disadvantages
<ul style="list-style-type: none"> • Low enzymatic activity • Partially bypass the liver • High dose is possible by enemas • Suitable to use in unconscious patients • Not limited by emesis 	<ul style="list-style-type: none"> • Low fluid volume for dissolution • Privacy concerns and culture barriers • Requires proper training • Leakage • Presence of faeces reduces drug absorption • Caregivers are unable or unwilling to administer

base (e.g. cocoa butter, hard fats) which is melted at body temperature, and hydrophilic base (e.g. gelatin, polyethylene glycol) which is dissolved in rectal fluid to release the drug [106,114]. The choice of suppository base depends on the physicochemical properties of the drug as well as the compatibility between drug and base. Surfactants (e.g. Polysorbate 80, Tween 20) may be incorporated into the formulation to enhance the wetting properties of the suppository with the rectal fluid, thereby increasing dissolution rate. Apart from the commercially available formulations, suppositories can be extemporaneously prepared by pharmacists.

5.4.2. Enema and rectal catheter

An enema is a liquid dosage form, either as solution, suspension or emulsion, for rectal administration. A micro-enema is an enema of volume below 5 ml. Enemas are mainly used for delivering laxatives and anti-inflammatory drugs. Typically, enemas or micro-enemas are administered from a plastic squeeze bottle or tube through an applicator into the rectum. They are generally absorbed more rapidly than suppositories, especially in patients who are dehydrated. However, there can be problems with leakage or bloating, which are associated to the volume of liquid being administered.

In recent years, some hospices have started to use a specialised rectal catheter (Macy Catheter®), an FDA-approved medical device, to deliver fluids and medications to control symptoms such as pain and nausea of patients in palliative care [115]. The catheter tip is inserted past the rectal sphincter and a small balloon is inflated inside the rectum to hold the catheter in place (Fig. 4). The catheter can stay in the rectum for up to 28 days to allow repeated drug administration without reinsertion, reducing any discomfort that may be experienced by the patients with each insertion. The device also allows drugs to be administered in a discreet manner. Moreover, stool in the rectum does not prevent the use of a rectal catheter unless the patient is suffering from diarrhoea. Drugs that can be absorbed rectally can be administered as a micro-enema through this method. If a liquid dosage form is not available, oral tablets can be crushed into fine particles and suspended in a small volume of water for rectal administration [112]. This practice of dosage form manipulation is currently more commonly adopted in paediatric than adult palliative care when no suitable alternative is available [116]. It enables the use of oral medications that are readily available at the bedside although the evidence of dosing and efficacy remains uncertain. Studies show that the use of a rectal catheter does not induce discomfort for the patients and is a cost-effective way to manage symptoms of patients in palliative care and should be further promoted [88,89]. The major concerns with the use of a rectal catheter is the lack of information regarding rectal pharmacokinetics and oral-to rectal dose conversions, which require further research.

5.4.3. Rectal gel

Rectal gel is the most common semi-solid dosage form for rectal drug delivery. This dosage form contains a high percentage of water which is trapped within a polymer matrix. The viscosity of the gel can be modified by the use of a co-solvent such as glycerin or propylene glycol. Using a high viscosity preparation minimises the problem of leakage which is often associated with enema use. A rectal gel requires the use of

an applicator for administration. One example of a rectal gel formulation is Diastat Acudial, a diazepam gel approved by the FDA for the management of epilepsy [31]. It is provided in a prefilled unit-dose rectal delivery system with the flexibility of dose adjustment [30]. The diazepam rectal gel demonstrated good safety and efficacy in the management of seizures in children and adults [117,118]. In addition, thermo-sensitive gel formulations using polymers such as poloxamers are being developed to allow the formulation to remain in a liquid state at room temperature for the ease of application, but undergo gelation at body temperature in order to prolong retention time, with reduced leakage [119–121].

6. Conclusions and future perspectives

Transmucosal routes of administration are promising alternatives for delivery of medications for rapid symptom relief in palliative and end-of-life care, due to their ease of administration and their ability to bypass (at least partially) first-pass metabolism. Each of the transmucosal delivery routes discussed in this review has its own advantages and disadvantages. They also share some similar challenges, suggesting that a drug that can be delivered by one transmucosal route may be suitable for administration via another transmucosal route. Such drugs should typically have a high potency with a small molecular weight, high lipophilicity and good aqueous solubility.

While buccal and sublingual routes rely on the use of specific dosage forms, intranasal and rectal routes can make use of the currently available preparations. This becomes particularly useful in emergency situations such as the COVID-19 pandemic where an immediate alternative route may be required. In this context, family members can be trained and supported to administer end-of-life drugs, although the potential significant emotional burden involved needs to be considered [9]. A parenteral formulation can be administered as a nasal spray by utilising a mucosal atomization device. Similarly, drugs that can be absorbed through the oral route can usually be absorbed through the rectal mucosa, offering the rectal route as a highly flexible and practical route of drug administration. Using a rectal catheter, drugs of different dosage forms can be delivered, including liquids and tablets which can be crushed, resuspended and administered as enemas. Compared to other transmucosal routes, the rectal route of administration is often neglected due to cultural barriers, privacy and dignity concerns and lack of professional confidence, partly due to a paucity of evidence for doses and efficacy. Currently, there is a lack of information regarding the pharmacokinetics of transmucosal drug administration in comparison to oral or parenteral drug administration. Comprehensive studies to generate data to order to provide clear guidance on dose conversion between different routes of administration is paramount to widen the use of transmucosal drug administration. Moreover, the epithelial barriers at mucosal surfaces have limited the number of drugs that are suitable for transmucosal delivery. Research on the development of transmucosal delivery system, such as the identification of safe and effective penetration enhancers and the use of nanoparticulate systems to control drug release could broaden the pool of drug choices. The recent pandemic has highlighted that it is time to revisit the potential of all of these transmucosal routes of administration and promote their use in palliative care. The experience with needle-free administration in paediatric palliative care could be usefully be extended to adult palliative and end-of-life care practice.

Declaration of Competing Interest

IW was the founder of Therakind Ltd. (a spin-off company of UCL) which developed the licensed buccal midazolam and licensed intranasal diamorphine. IW received funding from NIHR (PB-PG-0317-20,036) for DIPPER (Diamorphine Paediatric Palliative Evaluation of feasibility of Randomised controlled trial) study.

Acknowledgements

JL would like to thank Seed Funding for Strategic Interdisciplinary Research Scheme, The University of Hong Kong for financial support. SB is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East of England (ARC EoE) programme. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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